Anti-PSMA Immunotoxins

Novel Targeted Therapeutics for Prostate Cancer

Technology

The Prostate Specific Membrane Antigen (PSMA) has been proven to be an excellent target for prostate cancer therapy. It is highly expressed by virtually all prostate cancers and upregulated in advanced stages and metastases. We have generated several monoclonal antibodies (mAbs 3/A12, 3/E7 and 3/F11) and single chain antibody fragments (scFv A5 and D7) against cell adherent native PSMA. By genetically fusing Pseudomonas Exotoxin (PE40) to the scFv, the recombinant immunotoxins A5-PE40 and D7-PE40 could be produced. They specifically bind to and kill PSMA positive cancer cells in vitro. In a prostate cancer SCID mouse xenograft model it could be shown that A5-PE40 effectively inhibits the growth of PSMA expressing tumors.

Innovation

- A5-PE40 and D7-PE40 represent the first recombinant immunotoxins directed against PSMA
- These immunotoxins show a high and specific toxicity against PSMA expressing prostate cancer cells in vitro
- A5-PE40 could effectively inhibit the growth of PSMA expressing prostate cancers in a xenograft model in vivo

Application

- Novel immunotoxins against prostate cancer at all clinical stages
- Therapeutic option for adjuvant therapy of minimal residual disease

Market Potential

Prostate cancer is the most frequent malignant disease in men in the Western world. For the anti-PSMA immunotoxins as a new therapeutic agent we expect a huge market potential worldwide.

Responsible Scientist

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Anti-PSMA Immunotoxins – Novel Targeted Therapeutics for Prostate Cancer

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Background

No curative treatment currently exists for prostate cancer after progression beyond resectable boundaries. Therefore there is an urgent need for new treatment strategies.

The Prostate Specific Membrane Antigen (PSMA) is abundantly expressed on prostate cancer epithelial cells and even upregulated in androgen insensitive and metastatic disease. Thus a specific immunotherapy targeting this antigen is a potent novel therapeutic option for the management of this tumor.

Materials & Methods

Generation of A5-PE40

The gene sequence encoding a truncated form of \textit{Pseudomonas} Exotoxin A (PE40) was ligated in a C-terminal position to the anti-PSMA scFv A5. After periplasmic expression in \textit{E.coli} the immunotoxin was purified by immobilized metal affinity chromatography.

Binding to PSMA

The specific binding of the immunotoxin A5-PE40 to the extracellular domain of PSMA was investigated by flow cytometric analyses on PSMA expressing prostate cancer C4-2 cells with a mouse anti human c-myc mAb as detecting antibody.

Toxicity \textit{in vitro}

Toxicity of A5-PE40 \textit{in vitro} was determined using WST assays. The PSMA expressing prostate carcinoma cell line C4-2 was used as target and the PSMA-negative lines DU 145, PC-3, MCF-7 and HCT 15 as controls.

Antitumor activity \textit{in vivo}

Antitumor activity \textit{in vivo} was investigated in SCID mice bearing C4-2 tumor xenografts. Mice with DU 145 tumors were taken as controls. Each animal received 5 doses of 40 nM A5-PE40 or PBS within 12 days. Treatment effects were determined by a two-tailed, paired T-test for tumor volumes.

Results

\( \bowtie \) A5-PE40 was constructed as a recombinant protein consisting of the scFv A5 and PE40 with a human c-myc-tag and a His\(_x\)-tag.

\( \bowtie \) A5-PE40 shows specific binding to PSMA expressing prostate cancer cells.

\( \bowtie \) A5-PE40 shows a high and specific cytotoxicity against PSMA expressing prostate cancer cells \textit{in vitro}.

\( \bowtie \) A5-PE40 inhibits the growth of human PSMA-expressing prostate cancer xenografts \textit{in vivo}, while PSMA-negative tumors were not affected.

Conclusions

The recombinant anti-PSMA immunotoxin A5-PE40 shows potent and selective antitumor activity \textit{in vitro} and \textit{in vivo} in preclinical trials. Therefore it has the potential as a novel therapeutic agent for prostate cancer.

References

